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ANTIMONY TRIOXIDE IN THE TREATMENT OF EXPERIMENTAL TRYPANOSOMIASIS

BY

WARRINGTON YORKE

AND

B. BLACKLOCK

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In May, 1913, Kolle, Hartoch, Rothermundt and Schürmann published a preliminary report* of their investigations on the value of various antimony compounds in the treatment of experimental trypanosomiasis. A further account† of this work was published in August, 1913. As a result of an exhaustive examination of many antimony compounds—inorganic and organic—the authors arrived at the conclusion that in the trioxide they had discovered a remedy which, in respect of its chemo-therapeutic index and its permanent sterilising effects, far surpassed all others hitherto employed in the therapy of trypanosomiasis. It was with the object of examining this statement, and ascertaining if it applied in the case of larger animals, that the experiments recorded in this paper were performed.

In the earlier experiments the smaller laboratory animals (rabbits, guinea-pigs and rats) infected with various strains of trypanosomes were treated with one or more injections of antimony trioxide.

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*Ueber neue Prinzipien und neue Präparate für die Therapie der Trypanosomeninfektionen. Deut. Med. Wochenschr., 1913, May 1, Vol. XXXIX, No. 18, p. 825.

†Chemotherapeutische Experimentalstudien bei Trypanosomeninfektionen, Zeitschr. für Immunitatsf. und experiment. Therapie, 1913, August 5, Vol. XIX, No. 1, p. 66.

METHODS OF ADMINISTRATION

The drug was administered intramuscularly as a rule, but intraperitoneal and intravenous injection were also used in some cases. For the intramuscular injections 10 per cent. and 40 per cent. suspensions* of the drug in oil were prepared; for the intraperitoneal injections 1 per cent. suspension in 0·9 per cent. sodium chloride solution was used. As the latter suspension quickly deposited, it was found unsuitable for intravenous injection. In order to overcome as far as possible this difficulty, the drug was reduced by special means to an exceedingly fine powder which was suspended in distilled water. The suspension was allowed to stand in a cylinder for 18 hours, after which time the upper portion was decanted off. The amount of antimony trioxide contained in these suspensions was found to vary from 0·13 to 0·35 per cent. We are indebted to Mr. Prosper H. Marsden for kindly making this preparation.

The intramuscular method of administration possessed distinct advantages over the others, and was followed by much more beneficial results. By whatever method the drug was given, the amount absorbed was exceedingly small. Following intramuscular injection, the drug was found apparently unaltered, at the site of inoculation, six months later. In those animals in which it was given intraperitoneally yellowish white nodules consisting of small encapsuled masses of the drug were found in large numbers situated in the mesentery and omentum. Intravenous injection resulted in a deposit of the drug in the vein of the ear of rabbits used for injection, with the result that the vessel became plugged. This was due to the fact that the suspension in distilled water immediately deposited on contact with a fluid containing salt in solution.

One great disadvantage of the intramuscular method of injection was the frequency with which sterile abscesses formed. These, although rare in small animals, were very frequent in dogs and donkeys. In the latter animals even exceedingly small doses gave rise to abscesses; goats did not develop abscesses except after very large injections. Intravenous injection of the drug into the ear veins of rabbits gave rise to plugging as mentioned above, and

* We are indebted to Professor Kolle for kindly furnishing us with a supply of 'Trixidin.' This was used by us in our earlier experiments; later we prepared our own suspensions.

dry gangrene sometimes resulted with sloughing of portions of the ears. No ill effects were observed after intraperitoneal administration.

TABLE I.—Giving results of injecting normal animals with a suspension of Antimony trioxide.

No.	Animal	Amount of Sb_2O_3 given, in mg. per 10 g. of body weight	Day of death	Remarks
37	Donkey	0·2	15th	The drug was given in one place.
56	Dog	1·0	3rd	The drug was given in four different places.
57	,, ...	0·5	5th	The drug was given in two different places.
97	,, ...	1·0	8th	The drug was given in four different places.
98	,, ...	1·0	17th	The drug was given in one place.
99	,, ...	1·0	2nd	The drug was given in two places.

TOXIC EFFECTS OF THE DRUG

Small animals appear to be much more tolerant of the drug than large ones. In guinea-pigs, rabbits, rats and mice 1 mg. per 10 grms. of body weight could be given intramuscularly or intraperitoneally at a single injection without any ill effect, either local or general. Frequently very much larger doses were administered without any appreciable toxic effect. For example, in Table VIII it will be seen that Guinea-pig 8 received at a single injection 20 mg. per 10 grms. body weight, and remained alive for 40 days. The weight of the animal was unchanged until shortly before death. There was no abscess formation, and large quantities of the drug were found at the time of death, distributed between the muscle fibres at the site of inoculation. The drug was given prophylactically, and the animal inoculated subsequently with *T. rhodesiense*. We were unable to determine the cause of death, as trypanosomes were never found in the blood, and an animal inoculated from the guinea-pig at the time of death did not become infected. Many other examples of animals which lived for considerable periods after having received a single large dose of the drug are shown in the tables. We cannot state what is the

largest amount that can be given to small laboratory animals without causing toxic effects, but it is certainly much more than 1 mg. per 10 grms. body weight. It must be remembered, however, that only a minute fraction of the amount injected is absorbed, the vast proportion remaining unaltered at the site of inoculation. This probably accounts for the slight toxicity. Possibly the irregularity of the rate of absorption from the local depôt may explain the contradictory results obtained, both as regards host and parasites. On the other hand large animals, e.g., donkeys and dogs, are much more susceptible to the drug. Death resulted in several cases after the administration of doses of 1 mg. or less per 10 grms. body weight. Goats appear to tolerate the drug better.

TABLE II.—Giving the results of treatment with Antimony trioxide of small animals infected with *T. rhodesiense*.

No.	Animal	Day of treatment	Amount of Sb_2O_3 given, in mg. per 10 g. of body weight	Day on which trypanosomes disappeared from the blood	Day of relapse	Day of death	Remarks
7	Guinea-pig ...	15th	5·0	16th	...	31st	No relapse; animal died negative.
16	,,	8th	1·0	10th	...	111th	,, ,,
39	,,	10th	1·0*	11th	32nd	...	
		32nd	1·0*	33rd	...	84th	No second relapse; animal died negative.
40	,,	10th	1·0	12th	...	65th	No relapse; rat inoculated at time of death did not become infected.
41	,,	10th	0·8	11th	...	67th	No relapse; animal died negative.
42	,,	10th	1·0	12th	...	86th	,, ,,
76	,,	18th	1·0	20th	...	134th	,, ,,
77	,,	18th	1·0	22nd	...	85th	No relapse; rat inoculated at time of death did not become infected.
79	,,	13th	1·0	15th	117th	...	
		117th	2·0	118th	...	...	Animal alive and well on 137th day.
78	,,	13th	1·0	15th	...	120th	Trypanosomes never found in blood, but rat inoculated on 113th day became infected.
81	Rabbit	7th	1·0†	8th	27th	54th	

*Intraperitoneal injection of 1 per cent. suspension in saline solution.

†Injected intramuscularly in two separate regions.

THERAPEUTIC ACTION OF THE DRUG

The value of the drug was examined for a large number of different strains of trypanosomes, and remarkable variations in susceptibility to its effects were exhibited. As will be seen from Table II, a single intramuscular injection of 1 mg. per 10 grms. of body weight invariably sufficed to clear the trypanosomes from the peripheral blood, of guinea-pigs and rabbits infected with *T. rhodesiense*. As a rule there was no relapse, the animals living for periods varying from 34 to 134 days.

TABLE III.—Giving results of treatment of small animals, infected with *T. gambiense*, with Antimony trioxide.

No.	Animal	Day of treatment	Amount of Sb_2O_3 given, in mg. per 10 g. of body weight	Day on which trypanosomes disappeared from the blood	Day of relapse	Day of death	Remarks
4	Guinea-pig ...	44th	1·5	...	...	...	Trypanosomes almost invariably present in peripheral blood in large numbers.
		61st	0·6	...	...	...	
		67th	2·0	...	...	...	
		80th	0·6*	...	...	86th	
5	,,	26th	1·4	31st	...	38th	No relapse; animal (rat) inoculated at time of death did not become infected.
14	Rat	5th	4·0	...	...	14th	Trypanosomes always numerous in blood.
33	Guinea-pig ...	26th	2·0	...	...	...	
		32nd	1·6	35th	...	57th	No relapse after second inoculation; rat inoculated at time of death did not become infected.
53	Rat	6th	1·0*	...	...	...	
		11th	1·0*	...	...	...	
		15th	2·0	...	...	...	
		18th	1·0*	...	...	...	
		28th	2·0	...	...	...	
		37th	3·0	...	...	41st	Trypanosomes always present in peripheral blood in large numbers.
54	,,	6th	1·0*	...	...	...	
		11th	1·0*	...	...	...	
		15th	2·0	...	...	...	
		18th	1·0*	...	...	...	
		28th	2·0	...	...	30th	,, ,,
74	,,	3rd	2·0	...	...	...	
		5th	2·0	...	...	...	
		9th	4·0	...	...	16th	,, ,,

*Intraperitoneal injection of 1 per cent. suspension in saline solution.

Very different results were obtained on treating guinea-pigs and rats infected with *T. gambiense*. This strain† appears to be remarkably resistant to the drug, and in spite of the administration of relatively large and frequently repeated doses, the disease ran a normal course, trypanosomes generally being present in the peripheral blood in large numbers.

TABLE IV

A.—Giving the results of treatment of small animals, infected with *T. ugandae*, with Antimony trioxide.

No.	Animal	Day of treatment	Amount of Sb_2O_3 given, in mg. per 10 g. of body weight	Day on which trypanosomes disappeared from the blood	Day of relapse	Day of death	Remarks
6	Guinea-pig ...	25th	2	27th	164th	182nd	
18	Rat	7th	8	8th	...	15th	No relapse; animal died negative.

B.—Giving the results of treatment of small animals, infected with *T. brucei*, with Antimony trioxide.

No.	Animal	Day of treatment	Amount of Sb_2O_3 given, in mg. per 10 g. of body weight	Day on which trypanosomes disappeared from the blood	Day of relapse	Day of death	Remarks
13	Rat	3rd	6·5	5th	...	87th	No relapse; rat inoculated at time of death did not become infected.
34	Guinea-pig ...	22nd	1·0	...	...	26th	Trypanosomes did not disappear from blood.
44	Mouse	5th	1·0*	...	...	...	
		7th	2·5*	8th	...	24th	No relapse after second treatment; died negative.
45	,,	5th	1·0*	...	...	...	
		7th	2·5*	8th	32nd	...	
		35th	5·0	37th	49th	...	
		49th	10·0	50th	79th	79th	

†This strain was received by us from Professor Mesnil of the Pasteur Institute. He informs us that its origin was a case of sleeping sickness contracted in the French Congo. It was obtained from the patient (G. Y.) on December 23, 1904, and has since been preserved in laboratory animals. (See Bull. Soc. Path. Exot., June, 1912.)

C.—Giving the results of treatment of rats, infected with *T. evansi*, with Antimony trioxide.

No.	Animal	Day of treatment	Amount of Sb_2O_3 given, in mg. per 10 g. of body weight	Day on which trypanosomes disappeared from the blood	Day of relapse	Day of death	Remarks
43	Rat	10th	1*	11th	36th	38th	
52	,, ...	17th	1*	18th	25th	...	
		27th	2	28th	...	48th	No relapse after second treatment; died negative.

D.—Giving the results of treatment of rats, infected with *T. equiperdum*, with Antimony trioxide.

No.	Animal	Day of treatment	Amount of Sb_2O_3 given, in mg. per 10 g. of body weight	Day on which trypanosomes disappeared from the blood	Day of relapse	Day of death	Remarks
19	Rat	11th	4	12th	...	...	Animal alive and well on 238th day; rat sub-inoculated on 214th day not become infected.
49	,, ...	18th	1*	20th	97th	122nd	

E.—Giving the results of treatment of small animals, infected with *T. congolense*, with Antimony trioxide.

No.	Animal	Day of treatment	Amount of Sb_2O_3 given, in mg. per 10 g. of body weight	Day on which trypanosomes disappeared from the blood	Day of relapse	Day of death	Remarks
11	Rabbit	21st	5·0	23rd	...	...	Animal alive and well on 255th day; rat sub-inoculated on 231st day did not become infected.
48	Rat	20th	1·0*	21st	35th	...	
		35th	2·0	36th	54th	...	
		70th	2·5	72nd	151st	153rd	
72	Rabbit	7th	0·3	...	...	...	
		11th	0·3	...	...	13th	Trypanosomes did not disappear from the blood.

F.—Giving the results of treatment of small animals, infected with *T. equinum*, with Antimony trioxide.

No.	Animal	Day of treatment	Amount of Sb_2O_3 given, in mg. per 10 g. of body weight	Day on which trypanosomes disappeared from the blood	Day of relapse	Day of death	Remarks
47	Guinea-pig ...	35th	1·0*	36th	...	115th	No relapse; animal died negative.
69	Rabbit	30th	1·0	31st	46th	...	
		46th	0·25	47th	50th	...	
		50th	1·0	...	...	52nd	

The results of treating small animals infected with various trypanosomes pathogenic to domestic stock, viz., *T. ugandae*, *T. brucei*, *T. evansi*, *T. equiperdum*, *T. congolense*, and *T. equinum* are grouped together in Table IV. While the course of the disease appears to have been influenced in almost all cases, only two of the animals have survived up to the time of writing. Some remained negative for long periods after treatment, and died without parasites reappearing in their blood, whilst others relapsed after being negative for as long as 134 days.

*Intraperitoneal injection of 1 per cent. suspension in saline solution.

TABLE V.—Giving the results of treating with Antimony trioxide, goats infected with *T. vivax*.

No.	Day of treatment	Amount of Sb_2O_3 given, in mg. per 10 g. of body weight	Day on which trypanosomes disappeared from the blood	Day of relapse	Day of death	Remarks
1	38th	1·0	...	...	...	
	44th	2·5	...	...	45th	Trypanosomes did not disappear from blood.
2	8th	1·0	10th	...	22nd	No relapse ; animal died negative.
12	7th	4·0	8th	...	13th	,, ,,
17	11th	1·0	13th	15th	24th	
29	15th	0·25	...	...	...	
	18th	0·25	...	...	...	
	21st	0·25	23rd	27th	...	
	26th	0·25	28th	...	...	
	30th	0·25	...	32nd	...	
	32nd	0·06	...	...	...	
	33rd	0·06	33rd	...	...	
	35th	0·06	...	...	...	
	38th	0·06	...	...	193rd	No relapse after 33rd day;
31	16th	0·03	...	...	...	animal died negative;
	18th	0·03	19th	21st	...	diarrhoea.
	21st	0·03	22nd	...	...	
	26th	0·03	...	...	...	
	30th	0·03	...	...	198th	No relapse after 22nd day;
60	6th	0·06	...	...	...	animal died negative.
	7th	0·06	...	...	...	
	8th	0·06	...	...	...	
	9th	0·06	11th	13th	...	
	14th	0·06	...	...	...	
	15th	0·06	...	...	...	
	16th	0·06	...	...	...	
	18th	0·06	...	...	...	
	20th	0·06	...	...	...	
	22nd	0·06	23rd	...	...	
	24th	0·06	...	...	...	
	26th	0·06	...	...	...	
	30th	0·06	...	...	...	
	35th	0·06	...	...	...	
	42nd	0·06	...	124th	...	
	125th	0·06	...	...	...	
	127th	0·06	127th	...	140th	
70	29th	0·06	...	...	...	
	30th	0·06	...	...	...	
	31st	0·06	...	...	...	
	34th	0·06	...	...	...	
	35th	0·06	35th	...	...	
	39th	0·06	...	...	...	
	40th	0·06	...	...	...	
	41st	0·06	...	...	...	
	47th	0·06	...	...	116th	No relapse ; animal died negative.
73	33rd	0·06	...	...	...	
	34th	0·06	...	...	...	
	35th	0·06	...	...	...	
	36th	0·06	36th	...	...	
	38th	0·06	...	...	...	
	41st	0·06	...	...	...	
	48th	0·06	...	...	...	
	51st	0·06	...	...	134th	No relapse ; animal died negative.

The results of treating goats infected with *T. vivax* are given in Tables V and X. The best effects were obtained by repeated administration of small doses of the drug. Most of those animals which received one or two relatively large doses died in a short time either with or without trypanosomes in the blood. In all of the seven goats treated with small and frequently repeated doses, the course of the disease was greatly modified, and life was considerably prolonged. As a rule trypanosomes did not definitely disappear till six or eight doses of the drug had been given. Five of these goats died negative after periods varying from 109 to 198 days. Of the other two, one relapsed on the 124th day, and in spite of two further injections of the drug, died with trypanosomes in its blood on the 140th day. The other relapsed on the 184th day; it was again treated by repeated small doses. Trypanosomes disappeared from the blood, and were not found again; the animal died negative on the 201st day. The strain of *T. vivax* employed kills goats on an average in 30 days.

TABLE VI.—Giving the results of treatment of donkeys, infected with various trypanosomes, with Antimony trioxide.

No.	Strain of trypanosomes	Day of treatment	Amount of Sb_2O_3 given, in grammes	Day on which trypanosomes disappeared from the blood	Day of relapse	Day of death	Remarks
30	*T. rhodesiense*	18th	1·6	...	...	...	
		21st	1·2	...	...	...	
		23rd	2·0	...	...	...	
		28th	2·0	...	...	...	
		31st	0·2	...	...	...	
		32nd	0·2	33rd	...	...	
		34th	0·2	...	...	...	
		36th	0·2	...	...	...	
		38th	0·2	...	...	...	
		41st	0·2	...	...	56th	No relapse; animal died negative.
32	*T. equiperdum*	22nd	1·0	...	...	...	
		25th	2·0	...	...	...	
		33rd	0·2	...	...	...	
		34th	0·2	35th	...	...	
		36th	0·2	...	...	...	
		37th	0·2	...	...	...	
		40th	0·2	...	...	...	
		43rd	0·2	...	...	...	
		94th	0·1	...	...	147th	On 141st day a rat was inoculated and became infected.
68	*T. equiperdum*	48th	0·2	...	...	...	
		49th	0·2	...	...	...	
		50th	0·2	...	...	...	
		51st	0·2	...	...	...	
		54th	0·2	...	...	...	
		65th	0·2	...	...	...	
		66th	0·2	...	...	...	
		67th	0·2	...	...	...	
		70th	0·1	...	...	133rd	Rat inoculated on 132nd da did not become infecte

In Tables VI and XI are given the results of treating donkeys infected with *T. rhodesiense* and *T. equiperdum*. On the whole, the results obtained were unsatisfactory. Possibly owing to the fact that almost every injection gave rise to abscess formation, the drug exerted little influence on the number of parasites in the peripheral blood except in the case of Donkeys 32 and 60 infected with *T. equiperdum*. All the treatment animals became rapidly emaciated, and died sooner than the controls.

TABLE VII.—Giving the results of treating small animals, infected with *T. rhodesiense*, by intravenous injection of a suspension of Antimony trioxide in distilled water.

No.	Animal	Day of treatment	Amount of Sb_2O_3 given, in mg. per 10 g. of body weight	Day on which trypanosomes disappeared from the blood	Day of relapse	Day of death	Remarks
84	Rabbit	17th	0·1	18th	24th	...	
		26th	0·06	26th	...	...	
		29th	0·1	...	29th	29th	Animal died with convulsions at termination of the injection.
85	,, ...	25th	0·15	...	...	25th	,, ,,
87	,, ...	17th	0·1	18th	...	...	
		21st	0·1	...	29th	...	
		26th	0·05	...	...	...	
		36th	0·1	30th	39th	41st	
89	Guinea-pig ...	17th	0·25	18th	39th	...	
93	Rabbit	17th	0·1	18th	...	...	
		21st	0·15	...	...	...	
		26th	0·05	...	...	...	
		29th	0·1	...	...	31st	Trypanosomes did not reappear: animal died negative.
94	,, ...	11th	0·05	12th	...	...	
		13th	0·025	...	...	...	
		15th	0·05	...	17th	21st	
95	,, ...	17th	0·1	18th	...	...	
		21st	0·1	...	...	...	
		26th	0·05	...	...	...	
		36th	0·07	...	51st	...	
96	,, ...	9th	0·02	10th	13th	...	
		13th	0·04	14th	19th	...	
		19th	0·06	20th	...	...	
		24th	0·06	...	27th	...	
		27th	0·2	28th	34th	...	
		34th	0·2	...	...	39th	

Repeated intravenous injections of rabbits infected with *T. rhodesiense* were not attended by good results. As is shown in Table VII relapses were frequent, and trypanosomes only disappeared from the peripheral blood for short periods. Probably

this is accounted for by the fact already mentioned that the drug was deposited in the vein at the site of injection, the changes supervening preventing absorption.

TABLE VIII.—Giving the results of treating prophylactically, with Antimony trioxide, guinea-pigs subsequently inoculated with *T. rhodesiense*.

No.	Amount of prophylactic dose of Sb_2O_3 given, in mg. per 10 g. of body weight	Day on which parasites were injected intraperitoneally	Day on which trypanosomes appeared in the peripheral blood	Day of death	Remarks
8	20	Same day	...	...	
		29th	...	40th	Parasites never found; rat inoculated at time of death did not become infected.
9	5	Same day	...	...	
		29th	...	...	
		59th	...	118th	,, ,, ,,
20	4	5th	...	...	
		42nd	...	...	Parasites not found up to 221st day; rats inoculated on the 89th and 160th days after second inoculation of trypanosomes, have not become infected.
22	4	28th	...	49th	Parasites never found; rat inoculated at time of death did not become infected.
23	1	5th	...	...	
		35th	...	...	
		66th	131st	162nd	Animal died with parasites in blood.
24	1	14th	...	...	
		39th	82nd	178th	Only a few parasites seen on 82nd day and never again; rat inoculated from the guinea-pig on the 131st day did not become infected. The guinea-pig died negative.
25	1	21st	...	...	
		57th	69th	...	On the 70th day the animal was given a second dose of the drug equal to 1·5 mg. per 10 g. of body weight. Parasites disappeared two days later and never returned. The animal died negative on the 198th day; a rat inoculated from it on the 131st day did not become infected.

PROPHYLACTIC ACTION OF THE DRUG

A number of normal guinea-pigs and rats were injected intravenously with doses of antimony trioxide ranging from 1 mg. to 20 mg. per 10 grms. of body weight. After varying intervals they were inoculated with *T. rhodesiense* or *T. gambiense*. The object of these experiments was to ascertain the length of time during which a single dose of the drug would protect the animal against infection. The results obtained in the case of infection with *T. rhodesiense* are given in Table VIII, those with *T. gambiense* in Table IX. In the latter the drug had no protective action, a fact which corresponds with the resistance of this strain to treatment.

The incubation period was not increased, and subsequent treatment was without effect. Against *T. rhodesiense* infection there is evidence of distinct prophylactic action. For example, Guinea-pig 20 was inoculated on the 5th and 42nd days after receiving 4 mg. per 10 grms. of body weight of the drug into the muscle. It did not become infected, has increased in weight, and is alive and well 184 days after the second inoculation. Rats injected with its blood on the 89th and 160th days after the second inoculation did not become infected. Again the prolonged incubation period in Guinea-pig 23 is remarkable. This animal which had received 1 mg. per 10 grms. of body weight, was inoculated with trypanosomes on the 5th, 35th and 66th days following the prophylactic dose of the drug. Trypanosomes appeared for the first time on the 131st day, and it died with parasites in its blood on the 162nd day. Another interesting fact is obtained in the case of Guinea-pig 24. This animal had also received 1 mg. of the drug per 10 grms. of body weight intramuscularly. It was inoculated with *T. rhodesiense* on the 14th and 39th days. A few parasites were seen in its blood on the 82nd day; they disappeared next day, and did not reappear. The animal died negative on the 178th day, and a rat inoculated from it on the 131st day did not become infected. No prophylactic action against *T. vivax* was observed in goats, nor against *T. rhodesiense* in donkeys (see Tables X and XI).

TABLE IX.—Giving the results of treating, prophylactically and subsequently, with Antimony trioxide small animals inoculated with *T. gambiense*.

No.	Animal	Day of treatment after injection of trypanosomes	Amount of Sb_2O_3 given, in mg. per 10 g. of body weight	Day on which trypanosomes appeared in the blood	Day of death	Remarks
55	Guinea-pig ...	Day after	1·0	4th	...	
		11th	1·0	...	...	
		23rd	1·0	...	...	
		37th	1·0	...	68th	Parasites found in blood fairly constantly; animal died with numerous trypanosomes in its blood.
59	,, ...	Same day	1·0	13th	...	
		22nd	1·0	...	...	
		36th	1·0	...	77th	,, ,,
61	Rat	Same day	1·8	6th	...	
		7th	1·8	...	...	
		17th	1·8	...	...	
		25th	2·5	...	26th	Parasites constantly present in very large numbers.
62	,, ...	Same day	1·6	6th	...	
		7th	1·6	...	...	
		17th	1·6	...	18th	,, ,,
63	,, ...	Same day	1·6	6th	...	
		7th	1·6	...	9th	,, ,,
64	,, ...	Same day	1·5	6th	...	
		7th	1·5	...	...	
		17th	1·5	...	...	
		25th	2·0	...	...	
		35th	1·0*	...	...	
		39th	2·0	...	46th	,, ,,

*Intraperitoneal injection of 1 per cent. suspension in saline solution.

TABLE X.—Giving the results of treatment of goats, infected with *T. vivax*, with Antimony trioxide, prophylactically and subsequently.

No.	Day of treatment	Amount of Sb_2O_3 given, in mg. per 10 g. of body weight	Day on which trypanosomes disappeared from the blood	Day of relapse	Day of death	Remarks
26	14 days before	1·0	...	8th	...	
	9th	0·2	...	...	...	
	14th	0·2	...	...	17th	Trypanosomes constantly present in the blood.
27	21 days before	1·0	...	23rd	...	
	24th	0·05	24th	...	...	
	26th	0·05	...	...	...	
	27th	0·05	...	...	...	
	29th	0·05	...	...	...	
	31st	0·05	...	31st	...	
	32nd	0·05	32nd	...	...	
	33rd	0·05	...	...	...	
	35th	0·05	...	...	...	
	45th	0·05	...	...	...	
	52nd	0·05	...	...	109th	Trypanosomes never found after the 32nd day; animal died negative.
28	23 days before	1·0	...	22nd	...	
	24th	0·05	...	...	...	
	25th	0·05	...	...	...	
	27th	0·05	...	...	...	
	29th	0·05	...	...	...	
	30th	0·05	...	...	...	
	31st	0·05	31st	...	...	
	33rd	0·05	...	...	...	
	35th	0·05	...	...	...	
	43rd	0·05	...	...	...	
	49th	0·05	...	49th	...	
	50th	0·05	50th	...	...	
	51st	0·05	...	...	...	
	52nd	0·05	...	184th	...	
	184th	0·1	185th	...	...	
	187th	0·1	...	...	...	
	193rd	0·1	...	...	201st	Trypanosomes never found after the 185th day; animal died negative.

TABLE XI.—Giving the results of treating with Antimony trioxide, prophylactically and subsequently, donkeys infected with *T. rhodesiense*.

No.	Day of treatment after injection of trypanosomes	Amount of Sb_2O_3 given in grammes.	Day on which trypano-somes appeared in the blood	Day of death	Remarks
35	21 days before	2·0	9th	11th	
36	21 days before	2·0	9th	...	
	34th	0·2*	...	...	*Given in five different places.
	47th	0·2†	...	49th	†Given in two different places. Trypanosomes always present in blood.
65	18 days before	0·8*	8th	56th	*Given in two different places. Trypanosomes almost always found in blood.
66	18 days before	0·8*	8th	...	
	11th	0·1	...	...	
	12th	0·1	...	...	
	13th	0·1	...	...	
	14th	0·1	...	...	
	16th	0·4	...	...	
	18th	0·1	...	...	
	23rd	0·1	...	...	
	25th	0·1	...	...	
	27th	0·1	...	...	
	33rd	0·1	...	...	
	41st	0·2*	...	...	*Given in two different places.
	44th	0·2*	...	...	
	47th	0·4†	...	61st	†Given in four different places. Trypanosomes almost always present in blood.
67	18 days before	0·8*	8th	...	
	11th	0·1	...	...	
	12th	0·1	...	...	
	13th	0·1	...	...	
	14th	0·1	...	...	
	16th	0·4	...	...	
	18th	0·1	...	...	
	23rd	0·1	...	...	
	25th	0·2	...	...	
	27th	0·1	...	...	
	33rd	0·1	...	...	
	40th	0·3*	...	43rd	*Given in two different places. Trypanosomes almost always present in blood.

Except in the case of *T. gambiense* and *T. lewisi* the drug had an extraordinary effect in controlling the infection, so that the number of parasites found in the peripheral blood was usually very small. Frequently, as is shewn in Table XII, the peripheral blood remained free from trypanosomes for long periods.

TABLE XII.—Giving instances of relapse after long negative periods.

No.	Animal	Strain	No. of days in which peripheral blood was negative. Relapse period	Remarks
78	Guinea-pig	*T. rhodesiense* ...	98	Trypanosomes found by sub-inoculation.
79	,, ...	,, ...	102	
6	,, ...	*T. ugandae*	137	
49	Rat	*T. equiperdum* ...	77	
48	,, ...	*T. congolense* ...	79	
28	Goat	*T. vivax*	134	
60	,, ...	,, ...	101	
23	Guinea-pig	*T. rhodesiense* ...	65	
32	Donkey	*T. equiperdum* ...	106	Sub-inoculated rat became infected.

CONCLUSIONS

1. As regards the amount of antimony trioxide which can be given at a single dose without causing toxic effects, either local or general, it was found that, as is generally the case, a relatively much larger quantity is borne by small than by large animals. At least 1 mg. per 10 grms. of body weight can be administered intramuscularly, or intraperitoneally to rabbits, guinea-pigs, rats and mice without any untoward result. In donkeys and dogs, on the other hand, such a dose frequently caused death, and even much smaller doses were followed by abscesses at the site of inoculation.

2. Although the amount of drug administered can be regulated, we have, unfortunately, no control over the amount or rate of absorption. Post-mortem evidence proves that the proportion absorbed during a period of six months is exceedingly small. Probably this factor explains the somewhat unsatisfactory and contradictory results obtained.

3. In view of the extremely long periods after which relapses have occurred, we must be very cautious in stating that an animal is cured. But as several have remained negative without relapse for over 200 days, and subinoculated animals have not become infected, it appears that a certain number of cures have resulted.

4. Most of the strains used by us, viz., *T. rhodesiense*, *T. brucei*, *T. ugandae*, *T. evansi*, *T. equiperdum*, *T. congolense*, and *T. equinum*, appear to be very susceptible to the drug and trypanosomes disappear from the blood of infected animals within a couple of days of treatment. Our laboratory strains of *T. gambiense* and *T. lewisi* proved to be refractory.

5. Relapses after the blood had been negative for at least 100 days occurred in animals infected with *T. rhodesiense*, *T. ugandae*, *T. vivax* and *T. equiperdum*.

6. The drug exerted a definite prophylactic action when injected into guinea-pigs against subsequent infection with *T. rhodesiense*, but none against our laboratory strain of *T. gambiense*. No prophylactic effect was noticed in goats against *T. vivax* nor in donkeys against *T. rhodesiense*.

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